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COMPLETE SPECIFICATION

Acid Addition Salts of 2-Dimethylaminoethanol and Central Nervous System Stimulant Compositions containing them

We, RIKER LABORATORIES, INC., a corporation organised under the laws of the State of Delaware, United States of America, of 8480, Beverly Boulevard, Los Angeles, 48, California, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel acid-addition salts of 2-dimethylaminoethanol and to therapeutically-active compositions for producing central nervous system stimulation.

Acetylcholine is known to be an important hormone in activating the central nervous system. When this substance is applied to the exposed brain, animals have focal seizures which originate at the site of application. This seizure activity can be stopped by the administration of atropine, which is known to block some of the actions of acetylcholine. Efforts have been made to increase the amount of acetylcholine in the brain to obtain some degree of stimulation of mental activity by administering acetylcholine or choline to the patient. These efforts have been unsuccessful. These unsatisfactory substances have apparently failed to diffuse successfully through the two membranal barriers which protect the central nervous system. The first of these barriers is the blood-brain-barrier, which is an ill defined membrane around the capillary blood vessels which nourish the brain, and the second is the nerve membrane, which may prevent choline or acetylcholine from entering the nerve cell, where the choline would be synthesized into acetylcholine, which could perform its normal function of stimulating metabolism and the transmission of some nerve impulses.

That choline is ineffective in passing one or more of these membranal barriers is evidenced by the fact that choline chloride has no effect on the brain of man when given in doses as high as 6.0 grams per day. Choline chloride also does not produce epileptic seizures in rats nor does it have an effect on seizure thresholds of rats and mice when given in doses of 1.0 gm per kilogram of body weight daily for a period of 2 to 6 weeks.

In contrast with the negative results obtained with choline and acetylcholine, it has been discovered that 2-dimethylaminoethanol, and its acid-addition salts, and therapeutic compositions containing them, produce epileptic seizures in rats on chronic administration, lower the pentylenetetrazol seizure threshold in mice, and produce central nervous system stimulation in man with dosages of 5 to 500 milligrams per day (based upon weight of 2-dimethylaminoethanol base administered). This central nervous system stimulation in man is manifested clinically in prevention of migraine headaches, relaxation headaches, and the prevention of mental depression. Among other

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concomitant advantages in humans provided by therapeutic compositions in accordance with this invention are: relief of functional bowel distress, increase in peripheral circulation and a more regular menstrual cycle.

While it is not intended to rely upon any theory to explain the therapeutic effectiveness of the products and process of the invention, the scientific evidence available to date indicates that 2-dimethylaminoethanol, and its acid-addition salts first possess the property of readily diffusing through the two membranal barriers protecting the central nervous system and then secondly possess the property, once inside the membranes, of providing a precursor which is synthesized in the cells to acetylcholine. Presumably, the acetylcholine then provides the stimulation of the central nervous system.

By virtue of the ability of the novel chemical compounds and therapeutic compositions of the invention to stimulate the central nervous system and thereby prevent mental depression, a useful tool is provided in the treatment and cure of mental disorders in human beings. Human clinical trials conducted with the compounds and compositions of the inventions have provided significant relief from mental depression and a feeling of well-being in the patients and enabled them to think more clearly and in an organized way. In other patients relief from hypertension, headaches, irregular bowel habits, irregular menstrual cycle and general restlessness have been achieved.

It is an object of the present invention to provide novel acid-addition salts of 2-dimethylaminoethanol and novel therapeutically-active compositions containing an acid-addition salt of 2-dimethylaminoethanol or the free base as the active ingredient, which acid-addition salts and which compositions provide stimulation of the central nervous system.

The novel acid-addition salts of 2-dimethylaminoethanol in accordance with this invention are those of certain organic carboxylic and other organic acids. These acid-addition salts are particularly suitable for therapeutic use since they provide therapeutic compositions of excellent physical, chemical and therapeutic properties. They are generally weakly acidic, so that they do not produce the untoward results inherent in administering highly acidic substances to the patient. Among these suitable acid-addition salts of dimethylaminoethanol with an organic acid are: the lactate, acetate, ascorbate, nicotinate, citrate, neutral tartrate, acid tartrate, 3,4,5 - trimethoxybenzoate, *p*-acetylaminobenzoate, salicylate, ortho-, meta- or para-aminosalicylate, adenosinate, creatinate, succinate, fumarate, phthalate, *d*-pantothenate, *d*-pantoate, benzoate, propionate, pyruvate and beta-resorcylate salts.

The salts of ascorbic, nicotinic and pantothenic acids are particularly desirable since they also provide vitamin activity and may enhance the formation of acetylcholine in the cell. The salts of adenosine and creatine are advantageous because of the enzyme or nutritional properties imparted by the said moiety when these salts are administered. Novel dimethylaminoethanol salts of certain of the aromatic carboxylic acids are particularly suitable since they are substantially non-hygroscopic and yet will release 2-dimethylaminoethanol base for use by the body thereby permitting stimulation of the central nervous system. Among these salts are the beta-resorcylate, *p*-acetylaminobenzoate and *p*-aminobenzoate. These novel salts are substantially non-hygroscopic even when exposed to a relative humidity of about 50% for a period of 3 days. The *p*-acetylaminobenzoate is particularly outstanding since, in addition to being substantially non-hygroscopic, it is very soluble in water. The non-acylated *p*-aminobenzoate is also substantially non-hygroscopic, however, it is less suitable because of its reduced solubility in water. The lack of hygroscopicity of these salts provides important advantages in providing dry pharmaceutical products according to the invention.

Contemplated among the novel organic acid-addition salts are the salts or adsorbates of a cation exchange resin. Such cation exchange resins as "Dowex"-50 (a sulfonated copolymer of styrene and divinyl benzene) and "Amberlite" IRC-50 (a copolymer material having free carboxyl groups to provide the cation exchanging properties) may be employed for this purpose. The words "Amberlite" and "Dowex" are registered Trade Marks.

The therapeutic compositions of the present invention for producing stimulation of the central nervous system are dosage unit forms of pharmaceutical compositions, containing as the active ingredient, 2-dimethylaminoethanol or one of its acid-addition salts. These pharmaceutical compositions are desirable in unitary dosage form suitable for administration orally, by inhalation or parenteral injection. These compositions comprise tablets, capsules, injectable solutions, powders, syrup elixirs and aerosol compositions for inhalation therapy containing the active ingredient with a liquefied propellant fluid, such as one of the fluorinated lower alkanes.

By the term "dosage unit form" as used herein is meant a physically discrete unit containing an individual quantity of the active material in association with a pharmaceutical diluent or carrier, the quantity of active material being such that one or more units are required for a single therapeutic administration. It does not include solutions in water alone or other common solvents alone except when such are packaged in ingestible containers or have been prepared so as to be acceptable for parenteral injection. The active ingredient shall desirably be present in an amount of from 5 to 100 milligrams and

preferably 10 to 50 milligrams (based upon the weight of 2-dimethylaminoethanol base) for each dosage unit.

For parenteral injection the pharmaceutical compositions should contain the active ingredient in the form of a non-toxic acid-addition salt of 2-dimethylaminoethanol. In the case of pharmaceutical preparations suitable for oral or inhalation administration, either the 2-dimethylaminoethanol free-base or one of its non-toxic acid-addition salts may be employed.

In preparing the pharmaceutical compositions in accordance with this invention, acid-addition salts of 2-dimethylaminoethanol with either inorganic or organic acids may be employed. The acid employed is desirably one which is non-toxic to human beings at the dosage employed. Among the inorganic acids which may be employed in preparing the acid-addition salts of 2-dimethylaminoethanol are the mineral acid salts such as those of hydrochloric, phosphoric, sulphuric, hydrobromic and hydroiodic acids; either the neutral or acid salts may be prepared. Other inorganic acids which may be employed are thiocyanic, boric, carbonic and sulfurous acids.

Among the organic acids which may be employed are those which are non-toxic in the doses employed. Among these are lactic, acetic, ascorbic, gallic, nicotinic, citric, tartaric, *p*-acetylaminobenzoic, salicylic and 3,4,5-trimethoxybenzoic acids; adenosine, creatine; succinic, fumaric, ortho-, meta-, or para-aminosalicylic and phthalic acids; *d*-pantothenic, benzoic, propionic, pyruvic, and beta-resorcylic acids. Also the cation exchange resin adsorbates, such as those of "Dowex"-50 and "Amberlite" IRC-50 may be employed.

The acid addition salts of 2-dimethylaminoethanol contemplated for use in the present invention may be prepared by neutralizing 2-dimethylaminoethanol base with the corresponding inorganic or organic acid.

The central nervous system of mammals, and particularly humans, can be stimulated by administering 2-dimethylaminoethanol or its acid-addition salts of a non-toxic acid. As has been explained hereinabove, this base and its addition salts produce stimulation of the central nervous system as manifested by prevention of migraine headaches, relaxation headaches and the prevention of mental depression. There is also obtained relief of functional bowel distress, increase in peripheral circulation and a more regular menstrual cycle. The benefits are obtained by administering orally, by inhalation or by parenteral injection from about 5 to 500, or preferably 5 to 250, milligrams daily (based on weight of 2-dimethylaminoethanol base) of 2-dimethylaminoethanol or its acid-addition salt of a non-toxic acid where treatment of institutionalized schizophrenic patients are involved. In providing central nervous stimulant effect in the treatment of functional disorders, doses of 5 to 50 milligrams daily are suitable. The preferred dosage is from about 10 to 30 milligrams daily. For oral and inhalation therapy, either the base or an acid-addition salt may be employed. For parenteral injection it is desirable to employ an acid-addition salt of 2-dimethylaminoethanol. In amounts less than 5 milligrams daily the degree of stimulation may be insufficient, whereas in excess of 100 milligrams daily, the dosage may produce excessive stimulation. Preferably for adults, about 10 to 30 milligrams daily, and more preferably about 12 to 18 milligrams daily (based on the weight of 2-dimethylaminoethanol base) shall be employed. The optimum dosage is 15 mg. daily. For children it is desirable to employ less medicament and the desirable dosage is less than 3 mg. daily per 10 kilograms of body weight. These dosages are in contrast to the dosage of choline which the body will tolerate but without obtaining stimulation of the central nervous system. In the case of choline, 2,000 to 6,000 mg. per day may be tolerated without producing any substantial stimulation of the central nervous system. The process of providing stimulation of the nervous system may be practised by administering the pharmaceutical compositions according to this invention, which have been described hereinabove.

In the central nervous stimulant therapy employing 2-dimethylaminoethanol, and its salts, it has been discovered after clinical trials that there are certain biochemical adjuvants which assist in obtaining the therapeutic results which the present invention makes possible. Among these adjuvants are one or more of the following: *d*-pantothenic acid, pyridoxine, *l*-methionine and cyanocobalamin. The first three of these adjuvants are particularly suitable for oral therapy with dimethylaminoethanol, and its salts in tablet form. For intramuscular administration it is desirable to use a salt of 2-dimethylaminoethanol along with *d*-calcium pantothenate, pyridoxine and cyanocobalamin in a sterile aqueous solution.

It is believed that the adjuvant *d*-pantothenic acid assists in acetylating the 2-dimethylaminoethanol within the body. The adjuvant *l*-methionine is one of the body's important methylating agents and is useful in methylating the 2 - dimethylaminoethanol acetate into acetylcholine inside the cells of the brain. Cyanocobalamin is believed to act to keep the terminal sulfhydryl group of the co-enzyme A in the body reduced so that the reduced sulfhydryl group may assist in transferring an acetyl group to the 2-dimethylaminoethanol inside the brain cells. Pyridoxine is believed to assist in cleaving the thio-ethers in the body and in producing transmethylation reactions; both of which reactions are believed

to be involved in synthesizing acetylcholine from 2-dimethylaminoethanol inside the body cells.

In order more clearly to disclose the nature of the present invention, specific examples illustrating the preparation of products in accordance with this invention will hereinafter be described. Unless otherwise stated, the quantities of materials are referred to in terms of parts by weight.

EXAMPLE 1

About 26 grams of 2-dimethylaminoethanol were added with stirring to a solution of 50 grams of gallic acid dissolved in 200 ml. of methanol. The resulting 2-dimethylaminoethanol gallate crystallized readily and after being separated by filtration and washed with additional methanol, was dried under vacuum at 100°C. for two hours. The product weighed 65 grams and had a melting point of 178°C.

EXAMPLE 2

About 18 grams (0.2 moles) of 2-dimethylaminoethanol were added with stirring to a solution of 30.8 grams (0.2 moles) of beta-resorcylic acid dissolved in 100 ml. of isopropanol. Upon adding an equal volume of ether, the 2-dimethylaminoethanol beta-resorcylate precipitated. Upon being filtered and dried the 30 grams of crystals isolated were found to have a melting point of 118°C.

EXAMPLE 3

About 15 grams of tartaric acid were dissolved in 120 ml. of hot isopropanol. While still hot 8.9 grams of 2-dimethylaminoethanol were added to the solution and the solution was allowed to cool to room temperature overnight. The crystalline mass of 2-dimethylaminoethanol acid tartrate which formed was broken up, filtered, and washed with isopropanol. After the crystals were dried under vacuum at 45—50°C., they weighed 22 grams and had a melting point of 112—113°C.

EXAMPLE 4

About 15 grams of tartaric acid were dissolved in 12 ml. of water. To the resulting solution were added 8.9 grams of 2-dimethylaminoethanol and the solution permitted to stand overnight. The dimethylaminoethanol acid tartrate which crystallized was filtered off, washed with a small amount of water and dried at 45—50°C. under high vacuum. The yield was 7 grams and the salt had a melting point of 112—113°C.

EXAMPLE 5

About 13.1 grams of salicylic acid were dissolved in 25 ml. of hot isopropanol. While still hot, 8.9 grams of 2-dimethylaminoethanol were added to the solution and the solution permitted to cool. Then 10 ml. of ethyl ether were added and the dimethylaminoethanol salicylate which crystallized was filtered off, washed with a small amount of a mixture of isopropanol-ether (3:1) and dried. The yield was 21.5 grams having a melting point of 79°C.

EXAMPLE 6

The procedure of Example 3 was repeated, employing one-half as much tartaric acid. The resulting product was 2-dimethylaminoethanol neutral tartrate which was a liquid.

EXAMPLE 7

The procedure of Example 1 was repeated, replacing the gallic acid with 11.6 grams of fumaric acid and employing 8.9 grams of 2-dimethylaminoethanol and 120 ml. of isopropanol as the solvent instead of methanol. The solvent was removed by vacuum evaporation and residue first dried over potassium hydroxide pellets followed by drying over sulfuric acid. The resulting product was 2-dimethylaminoethanol acid fumarate crystals which had a melting point of 74°C.

EXAMPLE 8

The procedure of the preceding example was repeated, employing one-half as much fumaric acid, namely, about 6.0 and employing 60 ml. of isopropanol as solvent. The resulting product was 2-dimethylaminoethanol neutral fumarate which was a liquid.

EXAMPLE 9

The procedure of Example 1 was repeated, replacing the gallic acid with an equal molecular amount of creatine. The resulting product was 2-dimethylaminoethanol creatinate which had a melting point of 288—292°C.

EXAMPLE 10

The procedure of Example 1 was repeated, replacing the gallic acid with an equal molecular amount of succinic acid. The resulting product was 2-dimethylaminoethanol succinate which had a melting point of 173—178°C.

EXAMPLE 11

About 40 grams (0.223 mole) of *p*-acetylaminobenzoic acid was dissolved in 600 ml. of absolute methanol, and the solution was heated to reflux temperature. Heating was discontinued, and, with mechanical stirring, 19.9 grams (0.223 mole) of 2-dimethylaminoethanol was added through a dropping funnel as fast as the exothermic nature of the reaction permitted. The reaction mixture was allowed to cool to room temperature (2.5—3 hours) under mechanical agitation, and the solution was suction-filtered through "Celite" filter aid. The word "Celite" is a registered Trade Mark. The filtrate was poured into 500 ml. of anhydrous ethyl ether, seeded with a few crystals of 2-dimethylaminoethanol *p*-acetylaminobenzoate. The seeding crystals were obtained by introducing 3 to 6 drops of the filtered reaction mixture into a test tube containing 10 ml. of anhydrous diethyl ether. The contents of the test tube were thoroughly shaken and allowed to stand at room temperature. The salt crystallized out within not more than 10—15 minutes. The crude product (48.4 grams, 80.9% yield) was recrystallized from an absolute ethanolethyl acetate solvent system by suspending the salt in boiling anhydrous ethyl acetate and just

enough absolute ethanol was gradually added to effect solution after which the solution was concentrated to about two-thirds of the original volume on the steam bath, charcoal treated, and suction-filtered through "Celite" filter aid. The white crystals of 2-dimethylaminoethanol *p*-acetylaminobenzoate obtained, dried at room temperature at a pressure of 0.08 mm. Hg. for 15 hours, melted at 159.0—161.5°C.

EXAMPLE 12

About 32.7 grams (0.239 mole) of *p*-aminobenzoic acid was dissolved in 163 ml. of absolute methanol, and the solution was heated to reflux temperature. Heating was discontinued, and, with mechanical stirring, 21.3 grams (0.239 mole) of 2-dimethylaminoethanol was added through a dropping funnel as fast as the exothermic nature of the reaction permitted. The reaction mixture was allowed to cool to room temperature (2½ to 3 hours) under mechanical agitation, and the solution was suction-filtered through " Celite" filter aid. The filtrate was poured into 1000 ml. of anhydrous diethyl ether, seeded with a few crystals of 2-dimethylaminoethanol *p*-aminobenzoate from a previous preparation. Crystallization ensued immediately. The crude product (32.4 grams, 59.9% yield) was recrystallized from ethyl acetate. The recrystallized dimethylaminoethanol *p*-aminobenzoate, dried at room temperature under 0.08 mm. Hg. pressure for 15 hours, melted at 138—140°C. Due possibly to the interference of the unsubstituted amino group of the *p*-aminobenzoic acid during complex formation, the crystalline substance was found to contain dimethylaminoethanol in a lower than the calculated 1:1 molar ratio.

EXAMPLE 13

The procedure of Example 1 was repeated, replacing the gallic acid with 12.3 grams of nicotinic acid and employing 8.9 grams of 2-dimethylaminoethanol and 500 ml. of isopropanol as the solvent. The solvent was removed by vacuum evaporation at the temperature of a steam bath until the volume of the reaction mixture was reduced to about 250 ml. The vacuum evaporation was continued at room temperature. The resulting product was 2-dimethylaminoethanol nicotinate which was a syrupy liquid.

EXAMPLE 14

The procedure of Example 1 was repeated, replacing the gallic acid with an equal molecular amount of lactic acid. The resulting product was 2-dimethylaminoethanol lactate, which was a liquid.

EXAMPLE 15

The procedure of Example 1 was repeated, replacing the gallic acid with an equal molecular amount of acetic acid. The resulting product was 2-dimethylaminoethanol acetate, which was a liquid.

EXAMPLE 16

The procedure of Example 1 was repeated, replacing the gallic acid with 17.6 grams of ascorbic acid and employing 8.9 grams of 2-dimethylaminoethanol. The methanol solvent was removed by vacuum evaporation. The resulting product was 2-dimethylaminoethanol ascorbate, which was a syrupy liquid.

EXAMPLE 17

The procedure of Example 1 was repeated, replacing the gallic acid with an equal molecular amount of adenosine. The resulting product was 2-dimethylaminoethanol adenosinate, a syrupy liquid.

EXAMPLE 18

The procedure of Example 1 was repeated, replacing the gallic acid with an equal molecular amount of phthalic acid. The resulting product was 2-dimethylaminoethanol phthalate, a syrupy liquid.

EXAMPLE 19

About 5.7 grams (0.064 mole) of 2-dimethylaminoethanol in 5 ml. of water was neutralized to a pH of 6.4—6.8 with aqueous 10% sulfuric acid. To the solution was then added a solution of 15.25 grams (0.032 mole) of calcium *d*-pantothenate in 105 ml. of water. The resulting mixture was agitated and permitted to stand overnight. The calcium sulfate precipitate which formed was filtered and the water evaporated from the filtrate under reduced pressure at 25°C. The residue was subjected to a reduced pressure of 0.08 mm. of mercury for 46 hours. The residue, a yellow syrupy liquid, was dissolved in absolute methanol, the solution filtered and the methanol removed under reduced pressure. The residue was again dissolved in methanol and the methanol removed at reduced pressure. The resulting 2-dimethylaminoethanol-*d*-pantothenate was a yellow viscous material weighing 12.8 grams and having an optical rotation of plus 34.2°.

EXAMPLE 20

The procedure of Example 1 was repeated, replacing the gallic acid with 12.2 grams of benzoic acid and employing 8.9 grams of 2-dimethylaminoethanol with 25 ml. of isopropanol as the solvent. The solvent was removed by vacuum evaporation. The resulting product was 2-dimethylaminoethanol benzoate, a syrupy liquid.

EXAMPLE 21

The procedure of Example 1 was repeated, replacing the gallic acid with an equal molecular amount of propionic acid. The resulting product was 2-dimethylaminoethanol propionate, which was a liquid.

EXAMPLE 22

The procedure of Example 1 was repeated, replacing the gallic acid with an equal molecular amount of pyruvic acid. The resulting product was 2-dimethylaminoethanol pyruvate, which was a liquid.

EXAMPLE 23

The procedure of Example 1 was repeated, replacing the gallic acid with 19.2 grams of

citric acid and employing 8.9 grams of 2-dimethylaminoethanol with 16 ml. of isopropanol as solvent. The solvent was removed by vacuum evaporation. The resulting product was 2-dimethylaminoethanol di-acid citrate, a syrupy liquid.

EXAMPLE 24

The procedure of Example 1 was repeated, replacing the gallic acid with an equal molecular amount of *p*-aminosalicylic acid. The resulting product was 2-dimethylaminoethanol *p*-aminosalicylate which had a melting point of 71—72°C.

EXAMPLE 25

The procedure of Example 1 was repeated, replacing the gallic acid with an equal molecular amount of 3,4,5-trimethoxybenzoic acid. The resulting product was 2-dimethylaminoethanol 3,4,5-trimethoxybenzoate.

EXAMPLE 26

About 25 grams of "Dowex"-50 resin (in the hydrogen exchanging condition) was mixed with 10 grams of 2-dimethylaminoethanol and the resulting adsorbate was rinsed with water and dried.

EXAMPLE 27

About 11 grams of "Amberlite" IRC-50 (in the hydrogen exchanging condition) was mixed with 10 grams of 2-dimethylaminoethanol. The resulting adsorbate was rinsed with water and dried.

EXAMPLE 28

About 5.07 grams (0.039 mole) of 1-pantoyl lactone was hydrolyzed in 50 ml. of water containing 9.0 grams of barium hydroxide octahydrate over a period of 3 hours at a temperature of 73—81°C. The excess barium was removed as barium carbonate by bubbling carbon dioxide through the hot reaction mixture and filtering the precipitate. The filtrate, containing approximately 0.019 mole of barium pantoate, was added to a solution of 3.39 grams (0.038 mole) of 2-dimethylaminoethanol in 5 ml. of water, and the solution neutralized to a pH of 6.8 with aqueous 10% sulfuric acid. The reaction mixture was permitted to stand overnight. The resulting barium sulfate precipitate was filtered and water was removed from the filtrate under reduced pressure at 25°C. and the resulting residue evaporated under vacuum at 0.1 mm. of mercury for 16 hours. The residue, a yellow syrupy liquid was dissolved in absolute methanol and the solution filtered. The methanol was removed from the filtrate under reduced pressure at 25°C. and the solvent evaporated under vacuum. The dried residue was again dissolved in absolute methanol, filtered and again subjected to vacuum evaporation. The resulting yellow viscous material weighed 7.5 grams. The product, 2-dimethylaminoethanol *d*-pantoate, gave an optical rotation of plus 12.9°, indicating that the levorotatory lactone apparently yielded a dextrorotatory acid upon barium hydroxide hydrolysis.

EXAMPLE 29

A suitable formulation of tablets consists of:

	Milligrams per tablet
2-Dimethylaminoethanol acid tartrate (equal to 10 mg. of free base)	27.0
Milk sugar	50.5
Powdered sugar with 3% corn starch	50.5
Dicalcium phosphate	45.0
Corn starch USP (paste) (containing 10% water)	1.0
Calcium stearate	1.0
	175.0

The 2-dimethylaminoethanol salt was mixed with the milk sugar, powdered sugar and dicalcium phosphate and the mixture passed through a No. 30 screen. The screened mixture was granulated with the corn starch paste and passed through a No. 16 screen. The mixture was dried at 130—135°C. and passed through a No. 20 screen. The calcium stearate was added and mixed and the resulting mixture compressed into tablets weighing 175 mg. each.

EXAMPLE 30

A suitable formulation of an oral elixir consists of:

2-Dimethylaminoethanol beta-resorcylate	100 mg.
Elixir base to make 100 ml. volume.	

The elixir base contains orange spirits, sugar syrup, ethyl alcohol and distilled water.

When this formula is administered in 5 cc. doses, each dose contains about 5 mg. of medicament.

EXAMPLE 31

An illustrative example of preparing an aqueous solution for injection consists of placing 200 ml. of distilled water in a flask and adding 1 gram of 2-dimethylaminoethanol neutral tartrate with stirring, until solution is effected. The solution is filled into a clean, dry, 5 ml. ampule, and the ampule sealed and sterilized. Upon injecting the contents of one ampule, a dosage of 10 mg. of 2-dimethylaminoethanol neutral tartrate was administered.

EXAMPLE 32

A suitable formulation of a dry-filled capsule consists of:

2-Dimethylaminoethanol gallate	75 mg.
Lactose	75 mg.

The above ingredients were thoroughly mixed and placed in a hard gelatine capsule.

EXAMPLE 33

A suitable formulation of a soft gelatine capsule consists of:

2-Dimethylaminoethanol salicylate	10 mg.
Peanut Oil	200 mg.

The above ingredients were thoroughly mixed and enclosed in a soft gelatine capsule.

EXAMPLE 34

A suitable formulation for aerosol administration was prepared as follows:

About 3.25 grams of a solution containing 23.5% by weight of 2-dimethylaminoethanol in ethanol was cooled to minus 26°C. To this cooled solution was added 6.75 grams of a mixture of 61.5% by weight of dichlorodifluoromethane and 38.5% of dichlorotetrafluoroethane. The resulting mixture was sealed in a suitable container provided with a valve capable of discharging metered amounts of the material. The final mixture contained about 7.65% by weight of 2-dimethylaminoethanol hydrochloride, equivalent to about 5% of 2-dimethylaminoethanol free base.

EXAMPLE 35

This example illustrates a tablet form of medication for oral administration employing a biochemical adjuvant along with a form of 2-dimethylaminoethanol:

	Milligrams per tablet
2-Dimethylaminoethanol *p*-acetylaminobenzoate (equal to 20 mg. of base)	64.1
Pyridoxine	5.0
d-Calcium pantothenate	5.0
l-Methionine	200.0
Milk sugar	51.45
Powdered sugar with 3% corn starch	51.45
Dicalcium phosphate	45.0
Corn starch USP (paste) (containing 10% water)	1.5
Calcium stearate	1.5
	425.0

The 2-dimethylaminoethanol salt, pyridoxine, *d*-calcium pantothenate, and *l*-methionine were mixed with the milk sugar,, powdered sugar and dicalcium phosphate and the mixture passed through a No. 30 screen. The screened mixture was granulated with the corn starch and passed through a No. 16 screen. The mixture was dried at 130—135°C. and passsed through a No. 20 screen. The calcium stearate was added and mixed and the resulting mixture compressed into tablets weighing 425 mg. each.

EXAMPLE 36

This example illustrates a sterile injectible aqueous solution for intramuscular administration employing a biochemical adjuvant in com-

bination with a salt of 2-dimethylamino- ethanol:

2-Dimethylaminoethanol hydrochloride (equivalent to 20 mg. of base)	28.1 mg.
d-Calcium pantothenate	10.0 mg.
Pyridoxine	10.0 mg.
Cyanocobalamin	100 micrograms
Sterile distilled water	q.s. 1 ml.

Indicative of the nature of the central nervous system stimulation produced in mammals by the compositions in accordance with the invention are the results of a clinical testing program, which will now be described. After first determining the lack of toxicity of 2-dimethylaminoethanol as a result of extensive chronic toxicity studies in animals, a double-blind clinical study was conducted on 35 patients. These patients were subjected to therapy with tablets containing 10 mg. of 2-dimethylaminoethanol base as the tartrate salt and compared with an identical placebo. During the first week patients were given a dose of 1 tablet per day and for the second week the dosage was two tablets per day. Thereafter for a period of 3 months the subjects were allowed to increase, decrease or discontinue their medication at will, but during the last 6 weeks all subjects were given the 2-dimethylaminoethanol tablets. Significant subjective changes of the dimethylaminoethanol treated group were (1) increased muscle tone, (2) increased mental concentration and (3) changes in sleeping habits. In most cases the change in sleeping habits resulted in the patient requiring less sleep. Others reported sounder sleep with earlier, clear-minded awakening. A mood change in the patients to greater affability or mild euphoria coupled with a more out-going or out-spoken personality was noted. No significant changes occurred in heart rate, blood pressure, muscle strength, hand-steadiness, vital capacity and body weight, or the levels of fasting gastric acidity, protein bound iodine and blood cholesterol. In 25 of the 35 patients mental stimulation was noted which increased daily in the first week of medication and was greater than that of amphetamine. Unlike amphetamine, the stimulation lasted 24 to 48 hours after the discontinuation of the 2-dimethylaminoethanol and was not accompanied by a rebound period of depression.

WHAT WE CLAIM IS:—

1. A central nervous system stimulant composition in dosage unit form, as hereinbefore defined, comprising 2-dimethylaminoethanol or an acid-addition salt thereof as the active ingredient, and a pharmaceutical carrier.

2. A central nervous system stimulant composition comprising an acid addition salt of 2-dimethylaminoethanol, other than 2-dimethylaminoethanol gallate and 2-dimethylaminoethanol *p*-aminobenzoate, as the active ingredient, and a pharmaceutical carrier.

3. A composition according to claim 1 or 2, in which the acid-addition salt is that of an organic acid.

4. A composition according to claim 1 or 2, in which the acid-addition salt is that of an inorganic acid.

5. A composition according to any one of the preceding claims, in which the active ingredient is present in an amount of 5 to 100 milligrams per dose.

6. A composition according to claim 5, in which the active ingredient is present in an amount of 10 to 50 milligrams per dose.

7. A composition according to any one of the preceding claims, which also contains *d*-pantothenic acid, *l*-methionine, pyridoxine or cyanocobalamin.

8. A central nervous system stimulant composition in dosage unit form, substantially as hereinbefore described.

9. 2-Dimethylaminoethanol lactate salt.

10. 2-Dimethylaminoethanol acetate salt.

11. 2-Dimethylaminoethanol ascorbate salt.

12. 2-Dimethylaminoethanol nicotinate salt.

13. The neutral and/or acid salt of 2-dimethylaminoethanol citrate.

14. 2-Dimethylaminoethanol neutral tartrate salt.

15. 2-Dimethylaminoethanol acid tartrate salt.

16. 2-Dimethylaminoethanol salicylate salt.

17. 2-Dimethylaminoethanol adenosinate salt.

18. 2-Dimethylaminoethanol creatinate salt.

19. 2-Dimethylaminoethanol succinate salt.

20. The neutral and/or acid salt of 2-dimethylaminoethanol fumarate.

21. 2-Dimethylaminoethanol phthalate salt.

22. 2 - Dimethylaminoethanol *d* - pantothenate salt.

23. 2-Dimethylaminoethanol benzoate salt.

24. 2 - Dimethylaminoethanol propionate salt.

25. 2 - Dimethylaminoethanol pyruvate salt.

26. 2-Dimethylaminoethanol beta-resorcylate salt.

27. 2 - Dimethylaminoethanol *p* - acetylaminobenzoate salt.

28. 2 - Dimethylaminoethanol 3,4,5 - trimethoxybenzoate salt.

29. 2-Dimethylaminoethanol para-aminosalicylate salt.

30. A central nervous system stimulant composition comprising the acid-addition salt of 2-dimethylaminoethanol claimed in any of claims 9 to 29 as the active ingredient, and a pharmaceutical carrier.

31. An adsorbate of 2-dimethylaminoethanol on a cation exchange resin.

32. The acid-addition salts of 2-dimethylaminoethanol according to claims 9 to 29 and as hereinbefore described.

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